EXPERIMENTAL STUDIES ON EXTRACORPOREAL CIRCULATION USING PUMPOXYGENATOR WITH PARTICULA RREFERENCE TO THE EFFECT UPON BLOOD GASES, ACID-BASE BALANCE AND CARBOHYDRATE METABOLISM

AUTHOR(S):

YAMASAKI, HIDEKI

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By

HIDEKI YAMASAKI

From the 2nd Surgical Division, Kyoto University, Medical School
(Director: Prof.Dr. YASUMASA AOYAGI)

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INTRODUCTION

As in any field of modern therapy, advances in extracorporeal perfusion since 1937[1] have made an outstanding contribution to surgical managements for various cardiovascular disorders. Nowadays open heart surgery is carried out with considerably increased safety.

However, a number of problems referring to extracorporeal circulation still remain unsolved in spite of untiring efforts of many investigators.

That is, not a few obscure causes of death[2, 3] are present which seem to be ascribable to cerebral air embolism or cerebral damage.

Moreover, technical accidents and bleeding following cardiopulmonary by-pass are apt to occur frequently.[4] Recently, in order to ward off deaths coming from these causes, the so-called "Extracorporeal cooling"[5, 6, 7, 8, 9] device which is a combination of hypothermia and mechanical by-pass of the heart and lungs, is about to be practically employed in America. However, on the one hand, it is fundamentally important that we examine whether the heart-lung machines in use at present are truly efficient to limit the damage of blood constituents to a minimum, and to maintain the state of perfused subjects during the whole body perfusion as normal as possible. At first, we made an attempt at total cardiopulmonary by-pass utilizing a pulsatile pump and the WAUD-SALISBURY type foam oxygenator, but all experimental animals died of bleeding or in shock-like state during or after perfusion.

So, in order to bring these causes of death to light, we, at first, improved the heart-lung apparatus itself, the circuit and the method of preparation of priming blood and thus tried to keep the experimental animals alive without any accident. My colleague, ABE,[10] elucidated by his fundamental examination that hemolysis and diminution-rate of fibrinogen remarkably decreased by means of addition of ε-aminocaproic acid (antiplasmin agent) and polyvinyl-pyrrolidone (PVP) solution into siliconized collecting bottles, substitution of silicon rubber tube for vinyl-chloride tube, and application of silicon coating to the glass and metal parts in the circuit, and he showed also that plasmin activity was inhibited by addition of ε-aminocaproic acid.

Moreover, we tried to prevent post-operative bleeding by devising suitable operating methods and managements, especially by using cutting current in order to cauterize bleeding

points from the chest wall and by examining oxygenators in many ways. We then made a trial of partial perfusion without oxygenator. Next we tried to see whether the animals survived for a long time after partial perfusion with a few kinds of oxygenators. We then tried rapid hypothermia by A-A shunt without oxygenators, and finally succeeded in keeping all the experimental animals alive for long periods by means of 30-minutes total by-pass with vertical-double-cylinder oxygenators. This report deals with the improved points stated above and the experimental data, laying stress on long-term survival, with especial reference to blood gas changes, acid-base balance and carbohydrate metabolism during and after perfusion.

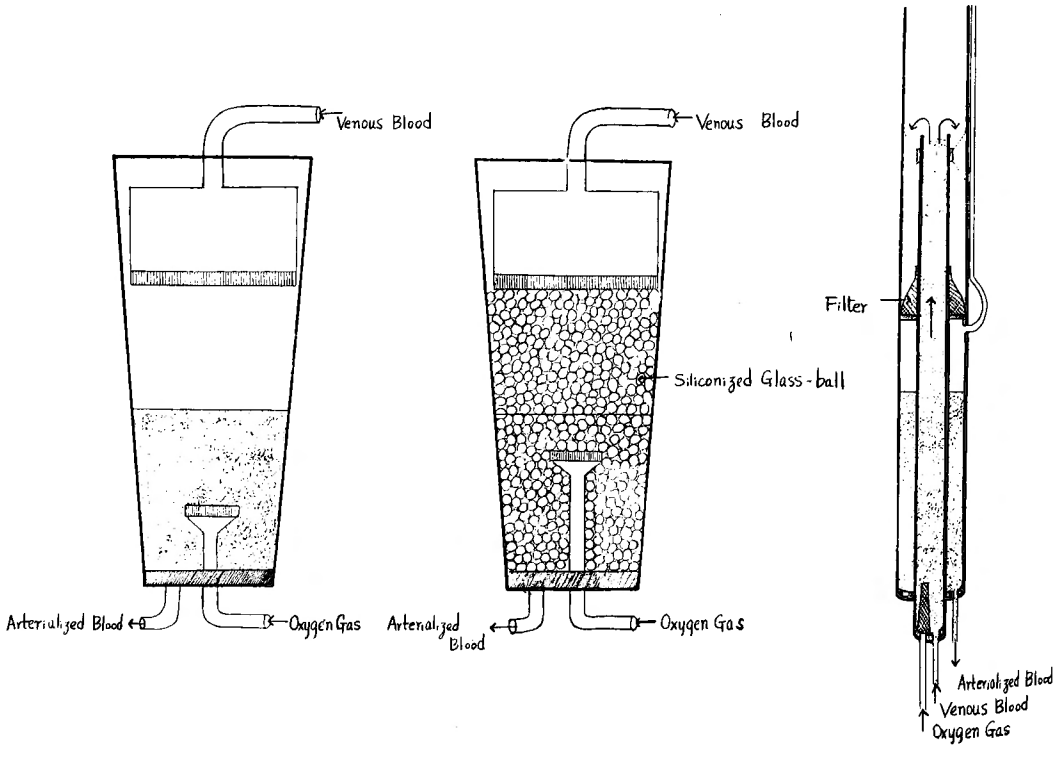
PROCEDURE

The procedure of this experiment is divided into the following four.

(1) Partial perfusion without oxygenator.
(2) Partial perfusion with oxygenator.
(3) Rapid hypothermia by A-A shunt.
(4) Total perfusion with oxygenaotr.

Apparatuses : In this experiment, as the artificial lung, we used the WAUD-SALISBURY type foam oxygenator,[11, 12] a sort of film oxygenator devised from the WAUD-SALISBURY type by filling it with a number of small siliconized glass-balls in order to prevent blood

Fig. 1 Kinds of Oxygenator used by us



constituents from destruction by stir of oxygen bubbles, and a vertical-double-cylinder bubble oxygenator made of plastic, designed by SAIGUSA[13] (Fig. 1). As the artificial heart, we used our pulsatile pump and Sigmamotor pump, for the purpose of comparison between these two. As the circuit, we used a silicon rubber tube or vinyl-chloride tube, and a bubble trap was inserted in a part of the circuit of silicon rubber tube just before an arterial cannula. In case of rapid hypothermia by A-A shunt, blood stream was cooled or warmed in the circuit by soaking a part of the silicon rubber tube into ice water or hot water in a thermoregulating box.

Preparation of priming blood : Without any anesthesia donor dogs were exsanguinated via a cannula inserted into a femoral artery two or three hours prior to the experiments. The blood was drawn into 500ml. siliconized collecting bottles containing 20mg. each of heparin to prevent coagulation.

In the course of these experiments, PVP-solution, antiplasmin agent and acid-citrate-dextrose (ACD) solution were added now and then into these bottles.

Materials : Adult mongrel dogs, weighing 5.5 to 13 kg, were used. The animals were used without any particular premedication, but in case of rapid hypothermia, premedication of 5 g. of Soya Lecithin, 100 mg. of Vit. E and 10 mg. of dimethyl-aminoethanol was daily given for a few days or a week before the operation, following the method described by Dr. HIKASA.[4, 5]

Anesthesia : Pentobarbarbital sodium, 20 to 25 mg. per kg. of body weight, intravenously, was used to anesthetize experimental dogs. An endotracheal tube was inserted, and respiration was maintained with intermittent positive pressure with pure oxygen and ether.

Methods : One mg. of atropine was injected into the experimental animals before operation, and heparin, 3 mg. per kg. of body weight, was given intravenously immediately prior to cannulation. The heparin effect was neutralized with protamine sulfate, 50 mg. to 100 mg., immediately after decannulation.

When ACD solution had been added into the priming blood, ACD blood was neutralized after perfusion, with calcium gluconate. In case of total body perfusion, the right hemithorax was opened at the fourth inter-costal space.

In case of partial perfusion by A-A shunt without oxygenator, for arterial delivery of blood, a metal cannula 2.5 mm. in diameter was inserted through the right or left carotid artery, and arterial return to the pump was through a large polyethylene catheter placed in the femoral artery.

In case of partial or total perfusion by V-A shunt with oxygenator, for arterial cannulation a metal arterial cannula was inserted through the femoral artery in a proximal direction, and for venous cannulation, two vinyl-chloride tubes 3-4 mm. in caliber were inserted, one through the jugular vein into the superior vena cava, the other through the femoral vein into the inferior vena cava.

Venous return was by means of gravity drainage to a reservoir. Oxygen 100 % without carbon dioxide was passed through the oxygenator, and the oxygen flow rate 1.5-2 liter per minute. On the occasion of total by-pass, the superior and the inferior venae cavae were encircled with tape tourniquets, and when the vertical-double-cylinder

oxygenator was used, blood levels in the oxygenator and in the venous reservoir indicated the state of balance of perfusion. Flow rate varied between 35 and 70 cc. per kg. of body weight per minute. The blood pH was measured by use of the SHIMADZU glass electrode at room temperature, and corrected at 37°c. P_{CO_2} and HOC_3^- were calculated from the VAN-SLYKE and SENDROY's nomogram,[16] and buffer base from the SINGER and HASTINGS' nomogram[17].

Hematocrit values were measured by the volume method. Blood viscosity was measured with a viscosimeter. Blood lactate and pyruvate were determined by the method of BARKER and SUMMERSON[18] and of FRIEDEMANN and HAUGEN[9,20], respectively. Blood sugar was determined by the method of NELSON-SOMOGYI.[21, 22]

Rectal and oesophageal temperatures were measured with thermometer.

Blood sampling: Arterialized blood for measurement was drawn off from the inferior part of an oxygenator. Venous blood for measurement was drawn from the venous cannulae.

EXPERIMENTAL RESULTS

(1) Partial perfusion without oxygenator:

We tried at first to clarify whether the animals survive for a long term (more than 48 hours) by partial perfusion with only a pump. Table 1 illustrates that Dogs No. 4, No. 5 and No. 6 died of severe bleeding despite 10 minutes' partial perfusion, as a result of the use of a vinyl-chloride tube as the circuit and priming blood withdrawal into non-siliconized collecting bottles.

Therefore, in cases of Dogs No. 7, No. 8, and No. 9, a bubble-trap, a metal cannula and the collecting bottles were siliconized, and a silicon rubber tube instead of a vinyl-chloride tube was employed. Then the tendency of bleeding completely disappeared, and these two animals except No. 8 survived for long periods. Accordingly, it may safely be said that both

Table 1. Partial Perfusion without Oxygenator

No.	Body Weight	Pump	Flow-rate	Perfusion Time	Bleeding Tendency	Result	Cause of Death	Improvement
4	12.6 kg	Pulsatile	15 cc/kg/min.	10 min	++	died (15h.)	Bleeding	
5	7.2	Sigmamotor	20	10	++	died (12h.)	Bleeding Filaria	
6	6.7	Pulsatile	25	10	++	died (5h.)	Bleeding	
7	8.5	Sigmamotor	35	10	−	survived		① Collecting Bottles ② Bubble Trap ③ Metal Cannula ∴ ①②③ Siliconized ④ Silicon Rubber Tube
8	8.7	Sigmamotor	35	10	−	died (3h.)	Filaria	
9	10.3	Pulsatile	30	10	−	survived		

Table 2. Partial Perfusion with Oxygenator

No.	Body weight	Pump	Oxygenator	Flow-rate	Perfusion Time	Nasal Secretion and Salivation	Result	Cause of Death	Improvement
10	5.9 kg	Sigmamotor	Waud-Salisbury Type	35 cc/kg/min	10 min	++	died (25h.)	unknown	
11	10.0	Pulsatile	Waud-Salisbury Type	35	10	−	survived		ε-aminocaproic acid, PVP added into priming blood
12	7.3	Pulsatile	Our Fil mType	25	10	−	survived		
13	6.6	Pulsatile	Our Film Type	45	10	−	died (26h.)	microbubble embolism	
14	7.5	Pulsatile	Our Film Type	50	10	−	survived		
15	9.9	Pulsatile (Sigmamotor)	Vertical-double-Cylinder Type	40	25	−	survived		

Table 3. Rapid Hypothermia by A-A Shunt

NO.	Body Weight	Pump	Flow-rate	Cooling Time	Suspending Time	Rewarming Time	Rectal Temperature (mininum)	Oesophageal Temperature (mininum)	Ventricular Fibrillation	Side of Cannulation	Result	Cause of Death
16	5.5 kg	Pulsatile	24 cc/kg/min	32 min	15 min	61 min	20 °C	15.8 °C	−	left carotid artery	died (7h.)	unknown
17	6.6	Pulsatile	22	33	13	87	24.5	18.5	+	left carotid artery	died (2h.)	weakening of heart
18	12.9	Pulsatile	23	51	15	75	25.7	23.0	−	left carotid artery	died (3h.)	unknown
19	7.8	Pulsatile	38	58	17	80	21.0	20.4	−	left carotid artery	died (5h.)	unknown
20	10.0	Pulsatile	28	45	10	53	24.3	22.9	−	left carotid artery	died (5h.)	unknown
21	9.0	Pulsatile	35	24	11	41	24.5	22.0	−	right carotid artery	survived	
22	6.0	Pulsatile	20	46	12	87	19.8	22.0	−	right carotid artery	survived	

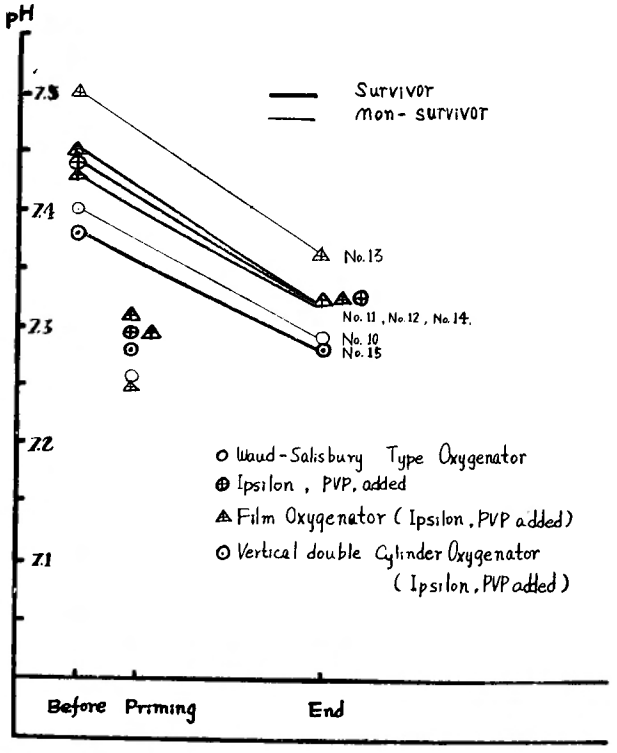
the pulsatile and Sigmamotor pumps are of value in general use.

(2) Partial perfusion with oxygenator :

According to the results above mentioned, we used mainly our pulsatile pump. But in Dog No. 10, the Sigmamotor pump was employed. As the artificial lung, in Dogs No. 10 and No. 11, the WAUD-SALISBURY foam oxygenator was used. In Dogs No. 12, No. 13 and No. 14, our film oxygenator which is a modification of the WAUD-SALISBURY type was used. In Dog No. 15, a vertical-double-cylinder bubble oxygenator devised by SAIGUSA was used, and in this case a Sigmamotor pump was employed in the circuit from venous reservoir to this oxygenator (Table 2).

Although no remarkable tendency of bleeding was found in dog No. 10, nasal mucous secretion and salivation were found to be much in this animal. Even a slight bleeding from a wound of the nasal mucosa by insertion of the nasal tube lasted for a long time. These phenomena seemed to be due some toxic substance produced through the destruction of blood in the foam oxygenator. For the purpose of detoxication, in the case of the rest of the animals after No. 11, ε-aminocaproic acid and PVP solution were added into the blood collection bottles. Then, in those animals, such hypersecretion as recognized in Dog No. 10 was completely absent. In Dogs No. 12 and No. 14 our film oxygenator was used, but hypersecretion was not noted in either of them, and they survived for long periods. Dog No. 13 died of microbubble embolism. In case of Dog No. 14, we opened the chest-wall but intrapleural bleeding was not noted. Dog No. 15 survived for a long

Fig. 2 pH in 10-minutes Partial Perfusion with Oxygenator



period, though 25-minutes' partial perfusion had been carried out. The pH decreased by 0.1-0.15 in all animals. Noteworthy in this connection is Dog No. 15 whose pH decline was only 0.1 despite 25-minutes' partial perfusion (Fig. 2).

No significant difference in pH was observed between the addition and non-addition of the antiplasmin agent and PVP. However, in the WAUD-SALISBURY type oxygenator and in our film oxygenator, the presence of fibrin-clots was remarkably observed macroscopically. My colleague, ABE, clarified that the decrease in fibrinogen in these cases is intense.

In the vertical-double-cylinder bubble oxygenator, the presence of fibrin-clots was considerably less than in the two oxygenators above mentioned.

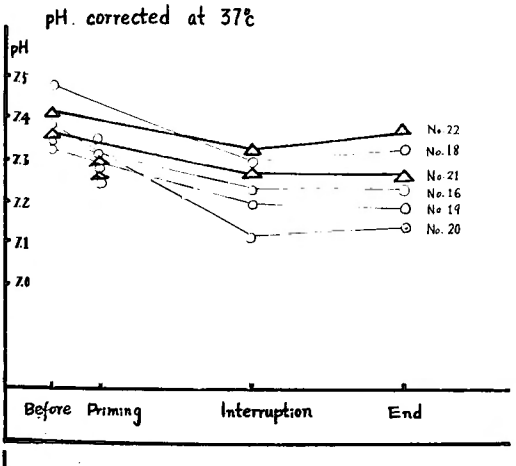
This is why we used this vertical-double-cylinder bubble oxygenator in the total by-pass which will be described herein later.

(3) Rapid hypothermia by A-A shunt :

Considering the weak points of the oxygenator above mentioned, and in order to cover the disadvantage of hypothermia by surface cooling at the same time, we tried rapid blood stream cooling without the use of the oxygenator.

As the preparatory procedure for this experiment, we gave daily 5 g. of Soya lecithin, 100 mg. of vit. E and 10 mg. of dimethylaminoethanol to the experimental animals for 3-7 days, following the recommendation by HIKASA.

Fig. 3



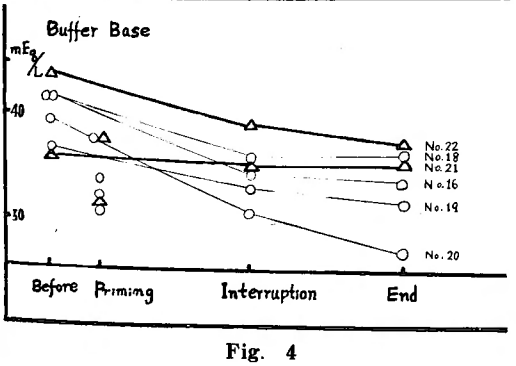
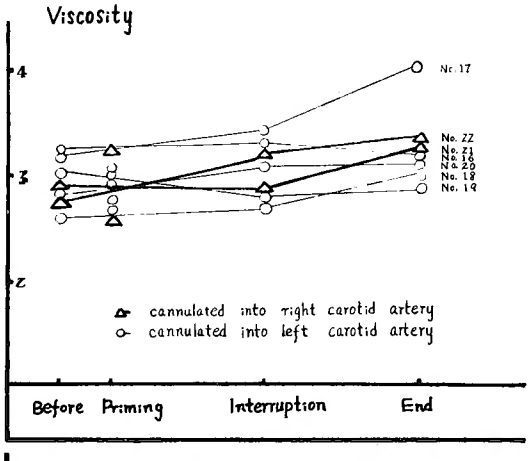


Fig. 4

Fig. 5



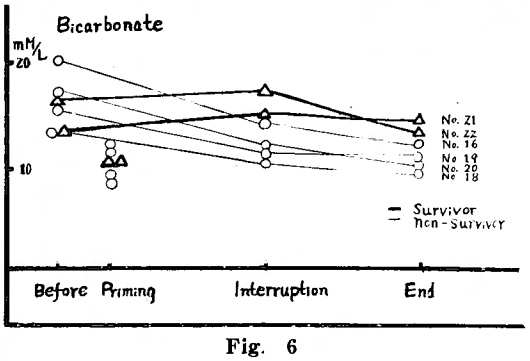


Fig. 6

We lowered the oesophageal temperature to as low as 15.8°c-23.0°c, halted the operation of the pump for a while, then we made the oephageal temperature rise nearly to normal. The result of this is shown in Table 3. Dogs No. 16 to No. 20, on cannulation into the left carotid arteries, all died of shock whose etiology is not clearly explained. Dogs No. 21 and No. 22, following cannulation into the right carotid arteries, survived for long periods.

Although pH (at 37.0°c) was lowered to acidity on interruption of perfusion (Fig. 3), It would rise to alkalinity when the value was corrected to one at the temperature of blood sampling. The degree of decrease in buffer base as shown in Fig. 4, was moderate in surviving animals, on the contrary, the decrease was intense in the animals that died, probably due to the protracted perfusion especially in Dog No. 20. As shown in Fig. 5, remarkable increase in blood viscosity was noted in Dog No. 17, which we had been given the premedication for only 3 days. In other animals, no marked changes in blood viscosity were observed in both the cooling and rewarming process.

Base bicarbonate was also peculiar to the surviving animals, that is, it rather increased in the cooling process, while it decreased in the animals that died (Fig. 6). As Fig. 7 shows the levels of lactic acid in the arterial blood, the rate of increase was low in the surviving animals, and also in Dog No. 18 among the animals that died it was low. In Dogs No. 16 and No. 19, the level of lactic acid had already been high in the priming

Fig. 7

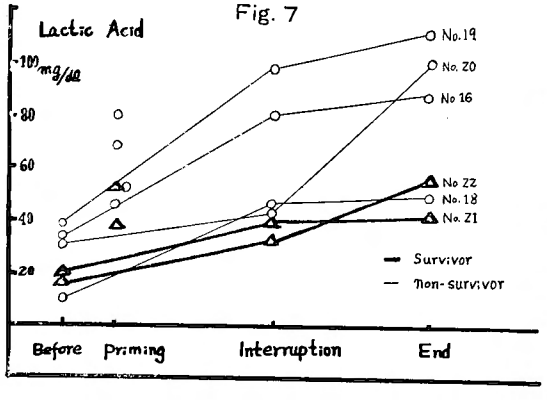


Fig. 8

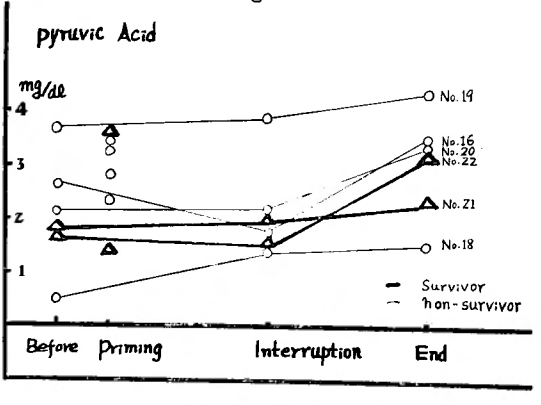


Fig. 9

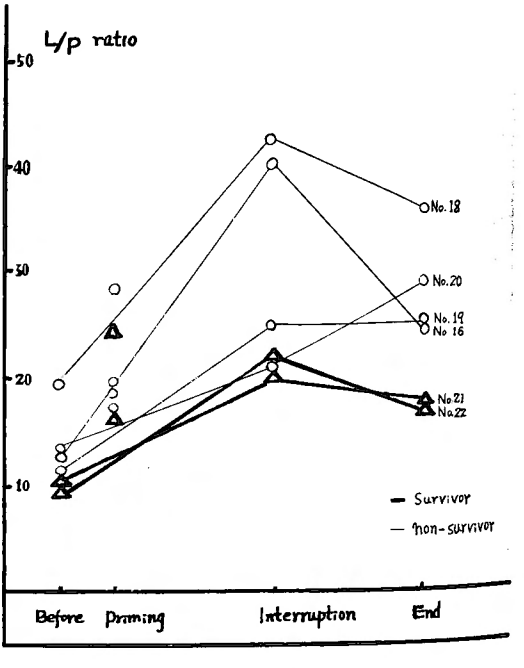


Table 4. Total Perfusion with Oxygenator

NO.	Body Weight	Oxygenator	Pump	Total Perfusion Time	Flow-rate	Result	Cause of Death	Improvement	measured case
23	8.5 kg	Our Film Type	Pulsatile	10 min	35 cc/kg/min	died	① Bleeding ② Hyperthermia		
24	7.5	Our Film Type	Pulsatile	10	35	died	①Bleeding ②Atelectasis oflung		○
25	6.3	Our Film Type	Pulsatile	10	40	died	① Bleeding ② Edema of lung		○
26	9.5	Our Film Type	Pulsatile	10	35	died	Technical Failure		
27	8.2	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	10	60	died	Injury of Vessels		○
28	7.8	Vertical-double-CylinderType	Pulsatile (Sigmamotor)	20	50	died	Bleeding		○
29	6.9	Vertical-double-Cylinder-Type	Pulsatile (Sigmamotor)	20	70	died	Bleeding		○
30	11.2	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	15	45	survived		using cutting current	○
31	7.5	Vertcal-double-Cylinder Type	Pulsatile (Sigmamotor)	15	40	died	Bleeding		○
32	8.0	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	15	45	died	Hypovolemia		
33	9.4	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	15	50	survived			○
34	7.5	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	15	40	died	Filaria		○
35	9.5	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	15	40	died	Filaria		
36	8.5	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	18	45	survived		Oxygenator siliconized	○
37	10.0	Vertical-doudle-Cylinder Type	Pulsatile (Sigmamotor)	15	50	survived		Oxygenator Siliconized	○
38	6.9	Waud-Salisbury Type	Pulsatile	15	50	died	Bleeding		○
39	9.0	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	30	55	survived		Oxygenator siliconized	○
40	10.0	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	60	43	died	unknown	Oxygenator siliconized	○
41	7.5	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	30	55	survived		Oxygenator siliconized	○
42	9.9	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	30	50	survived		①Oxygenatorsiliconized ②Keeping Priming Blood in Icebox	○
43	7.5	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	30	50	died	Technical Failure	①Oxygenatorsiliconized ②Keeping Priming Blood in Icebox	○
44	9.6	Vertical-double-Cylindre Type	Pulsatile (Sigmamotor)	30	50	survived		①OxygenatorSiliconized ②using ACD solution	○
45	9.2	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	60	55	died	unknown	①OxygenatorSiliconized ②using ACD Solution	○
46	9.5	Vertical-double-Cylinder Type	Pulsatile (Sigmamotor)	30	55	survived		①OxygenatorSiliconized ②using ACD solution	○

blood before the perfusion, and the rapid increase in it took place in the cooling process, probably due to its administration to the animals at the start of perfusion.

In Dogs No. 16 and No. 17, the perfusion began with the priming blood kept at room temperature. In other animals, the perfusion began with the priming blood warmed to the normal temperature of the body and cooled little by little after that. In these experiments, the gradual cooling method was preferable to the rapid cooling method, considering the danger of the oxygen-bubble embolism and in order to preclude the risk of overdosage of the lactic acid.

Pyruvic acid level changed almost in parallel with lactate level, and rapid increase in pyruvic acid level was especially seen in the rewarming process (Fig. 8). At the end of perfusion, in Dog No. 19 the value was as high as 4. 37. As shown in Fig. 9 the rapid increase in L/P ratio was seen in the cooling process. In Dogs No. 16 and No. 18 the ratio rose to as high as 40 during perfusion but in other dogs the ratio ranged between 20 and 25. In the case of the survivors, the ratio decreased to as low as from 16.8 to 17.8, and in Dogs No. 16 and No. 18, the ratio decreased to 24.8 and 35.7 while in Dog No. 19 and No. 20, the ratio rather increasd, probably due to the presense of relative hypoxia in the tissues in the process of rewarming. But at the end of perfusion, all the survivors showed the ratio of less than 20. The superiority of our pulsatile pump was demonstrated in Dog No. 20, though partial perfusion had been undergone, for it kept the experimental animal alive for a long period in the following condition :

The lowest rectal temperature……19.8°c ;
The lowest oesophageal temperature……22.0°c ;
The period of perfusion……133 minutes.

It is quite interesting to know that the experimental animals were kept alive only when cannulation had been made into the right carotid artery. It was also found desirable to perform hemodynamic examinations.

(4) Total perfusion with oxygenator :

In the first place, we tried total perfusion for 10 minutes using our pulsatile pump and our film oxygenator (Table 4). The result of this experiment was that all the experimental animals died of intrapleural bleeding and the atelectasis or edema of the lung.

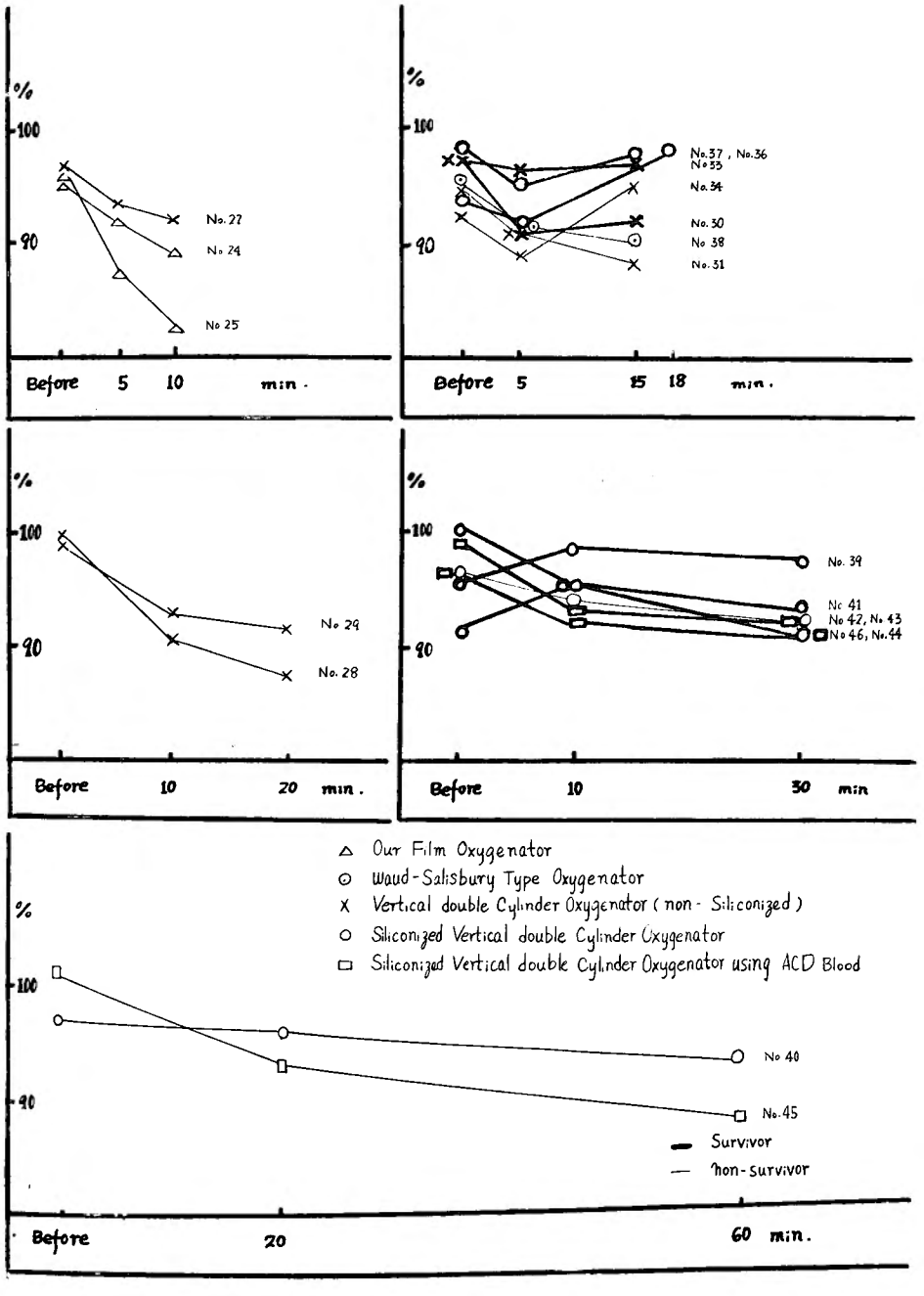
In the second place, we tried total perfusion using the vertical-double-cylinder oxygenator for 10-20 minutes, and all the experimental animals died of intrapleural bleeding. However, the result of studies by my colleague, ABE, had showed that coagulation factors in blood are not disturbed so much under these circumstances. Thus we came to the conclusion that the complete stoppage of bleeding from the wound of operation should be performed.

So, from the subsequent experiment onward, that is from Dog No. 30, we used the cutting current to cauterize the bleeding points of the wound of operation.

Here, we came to get the survivors in 15 minutes' total perfusion. In dogs after No. 36, each time we siliconized the inner surface of the virtical-double-cylinder oxygenator. This procedure led to the caquirement of more survivors. Thus we came to be able to make all the remaining dogs alive except No. 43, which died by the injury of the vessels.

We must say that in the animals after No. 44, 120 cc of ACD solution was added per 1500 cc of heparinized priming blood.[23, 24, 25] The interesting fact in this connection is that the ACD-added group awakened earlier than the non-ACD-added group. The auther examined the above mentioned facts from the viewpoints of changes of blood gases, acid-base equilibrium and carbohydrate-metabolism. The results of this examination are

Fig. 10 Arterial Oxygen Saturation during Perfusion



as follows :

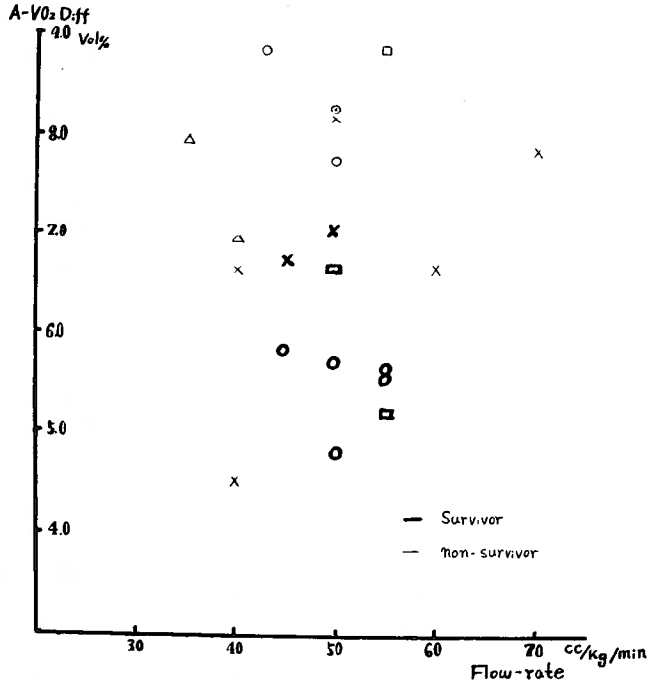
(A) Oxygen saturation of arterial blood :

Fig. 10 shows the value of arterial blood oxygen saturation measured immediately after blood was oxygenated in the oxygenator. We can say that every value is more than 90 % at the end of perfusion with the exceptions of Dogs No. 24 and No. 25 using our film oxygenator, Dog No. 31 using the vertical-double-cylinder oxygenator, and Dog. No. 45 using ACD blood in 60 minutes-perfusion. Therefore, we came to know that, with the use of our film oxygenator, there was a limit to the period of perfusion because oxygenation was not enough even in 10 minutes total perfusion, and that it was almost impossible to increase the blood flow. We came to know also that oxygen saturation decreased to as low as 90.4 % with the use of the WAUD-SALISBURY foam oxygenator. The survival rate was very high in the animals of 30 minutes perfusion with the vertical-double-cylinder oxygenator, which was due to the fact that the decrease in oxygen saturation during perfusion did not take plase so remarkably and that the oxygenation was well performed.

(B) Arteriovenous oxygen difference :

Although the arteriovenous oxygen difference varies with the blood flow rate (Fig. 11) and the condition of the experimental animals, we can say generally that in the

Fig. 11 Relationship between Arterio-venous Oxygen Difference and Flow-rate



instances of the survivors, the values are comparatively low (4.7-7.0 vol %) at the end of perfusion (Fig. 12), the cause of which would be attributed to perfusion at a comparatively low flow rate.

Fig. 12 A-VO_2 Diff

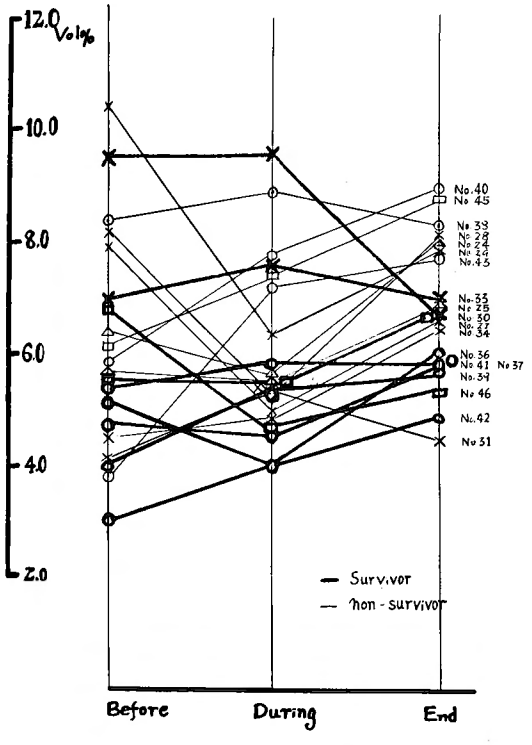
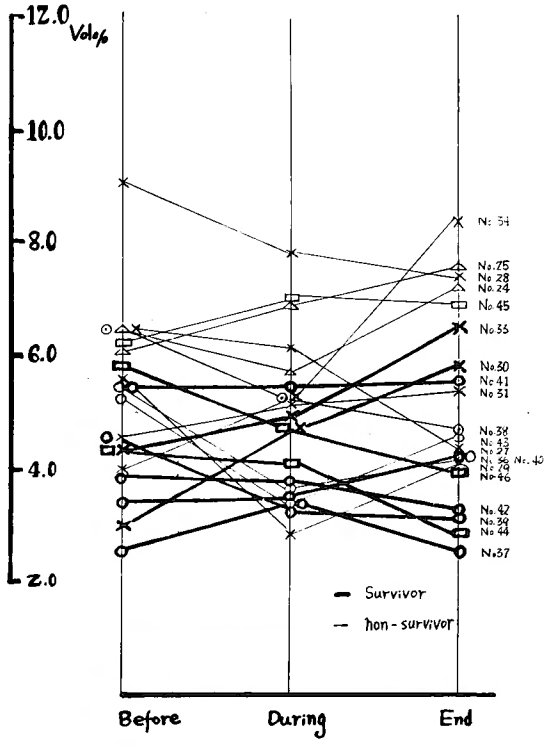


Fig. 13 A-VCO_2 Diff



(C) The arteriovenous carbon dioxide difference :

As is shown in Fig. 13, there were various tendencies according to the animals, but in the instances of the survivors, the values were from 2.7 to 6.6 vol % at the end of the perfusion.

(D) Oxygen consumption :

As is shown in Fig. 14, oxygen consumption increased or decreased in the course of the perfusion in each animal. In the survivors, oxygen consumption was 2.4-3.5 cc/kg/min. As for relation between oxygen consumption and flow rate, as shown in Fig. 15, the flow rate of survivors was 45-55 cc/kg/min and oxygen consumption corresponding to this flow rate ranged from 2.3 to 3.5 cc/kg/min. In this figure, we observe an approximately linear relationship between oxygen consumption and flow rate, but the survival rate does not always become higher in proportion to the oxygen consumption.

(E) oxygen saturation of mixed venous blood :

It is worthy of attention that, when the oxygen saturation of mixed venous blood was kept more than 55 % the survival rate rose, and that in almost all the cases of 30-minutes perfusion, venous oxygen saturation was kept more than 60 % at the end of perfusion (Fig. 16). Considering this oxygen saturation of mixed venous blood with reference to the flow rate, as shown in Fig. 17, an interrelation between the flow rate and venous oxygen saturation does not seem to be present. In this figure 17, the survivors are contained in a circle formed by the dotted line. From this interesting

Fig. 14 Oxygen Consumption during Perfusion

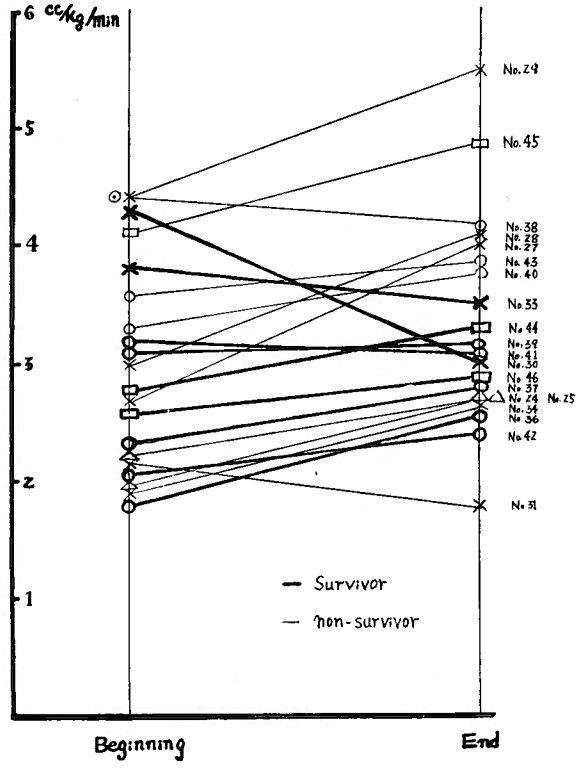


Fig. 15 Relationship between Oxygen Consumption and Flow-rate

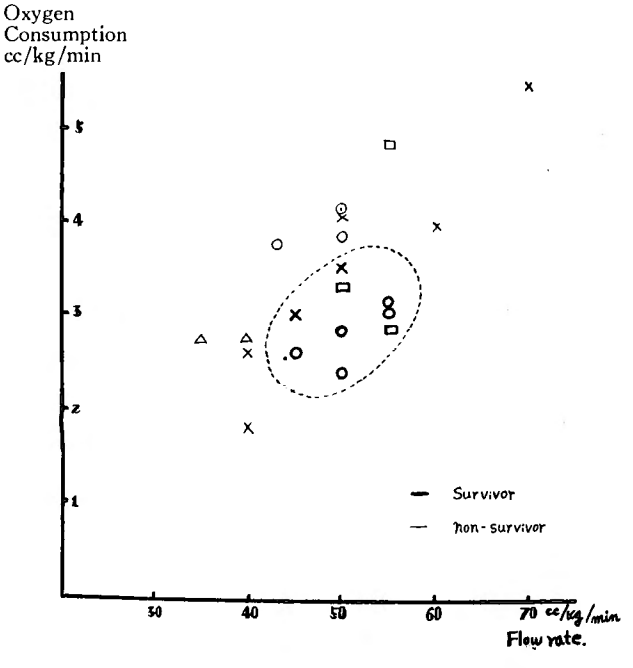
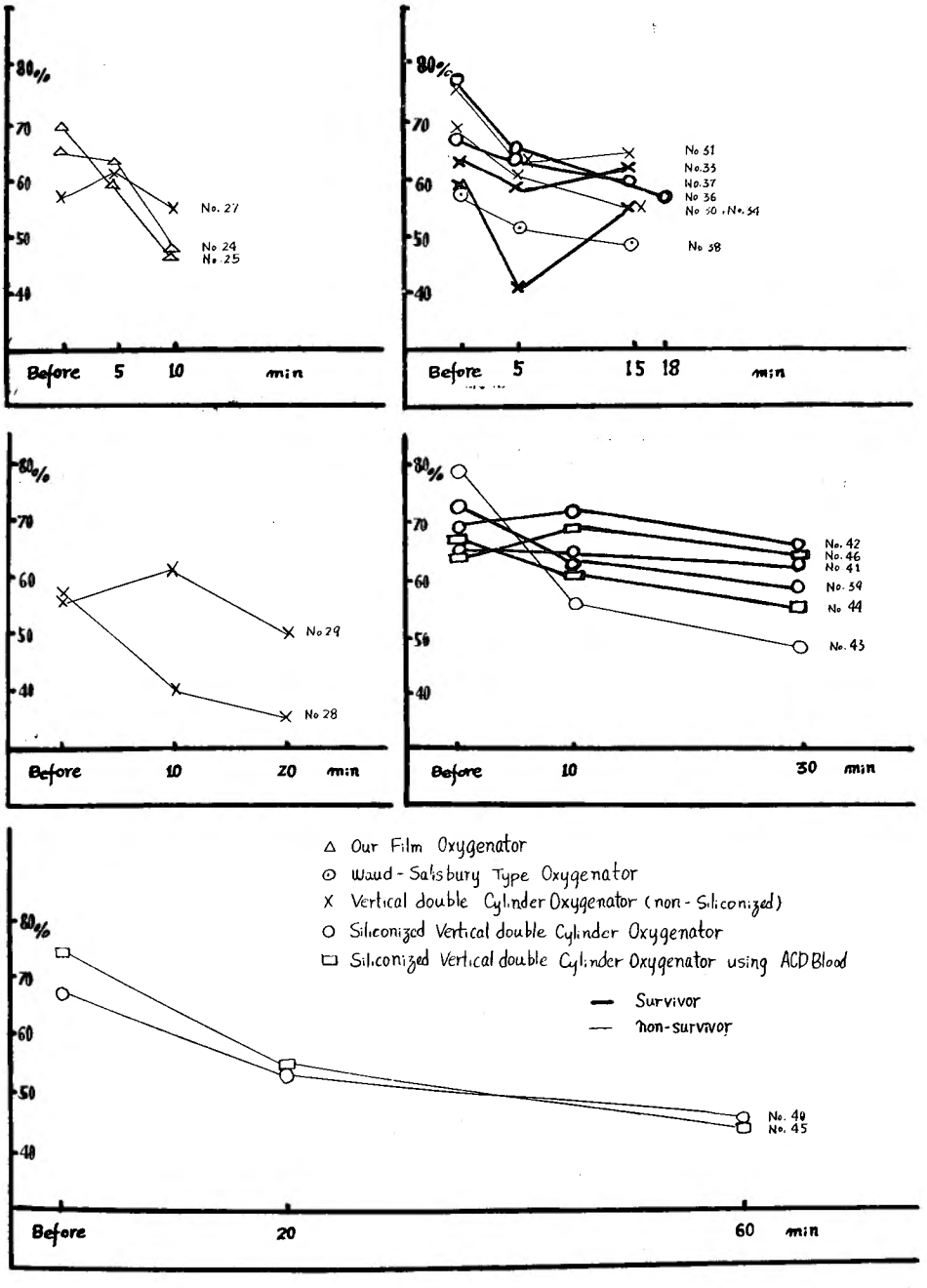


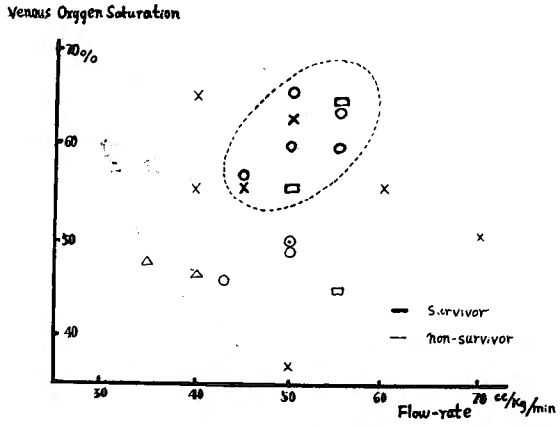
Fig. 16 Venous Oxygen Saturation during Perfusion



fact, we can presume that when flow rate of 45-60 cc/kg/min is used and venous oxygen saturation is kept more than 55 %, the survival rate will be far higher.

That is, under this condition, the oxygen demand of the animals will be almost fully supplied and there will not be anoxia in the tissues.

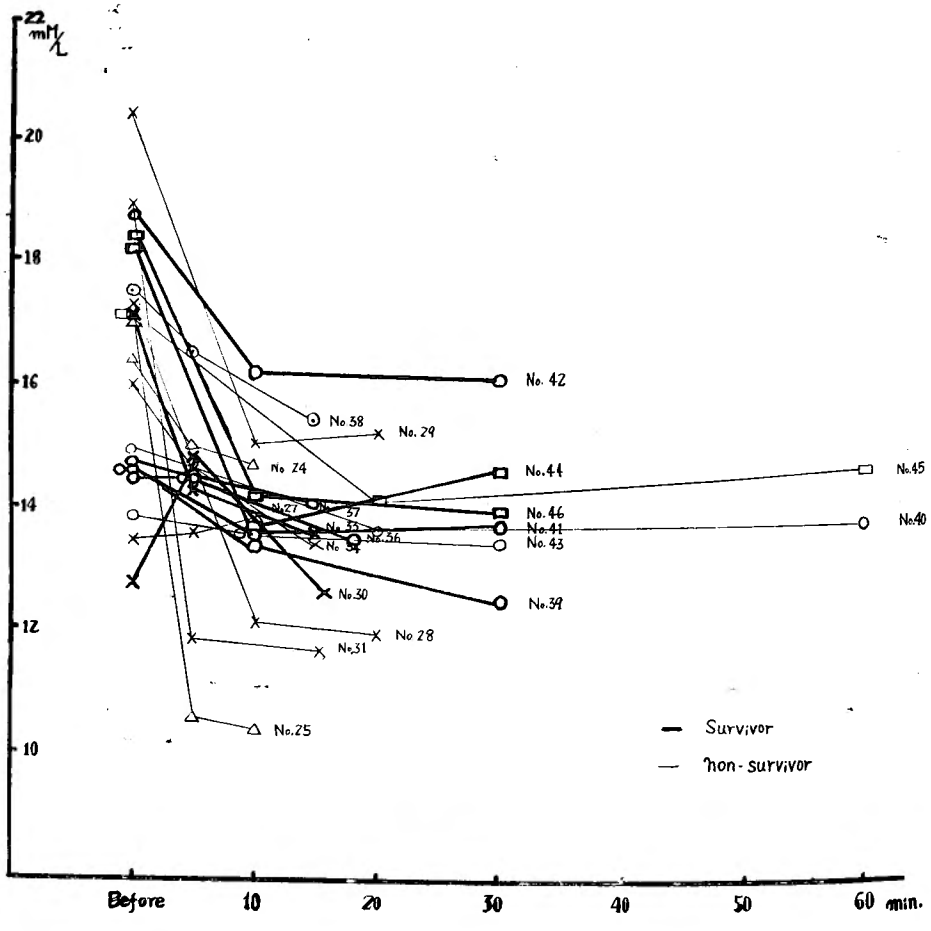
Fig. 17 Relationship between Flow-rate and Mixed Venous Oxygen Saturation



(F) Arterial carbon dioxide content :

The carbon dioxide content in arterial blood of the animals had already reduced

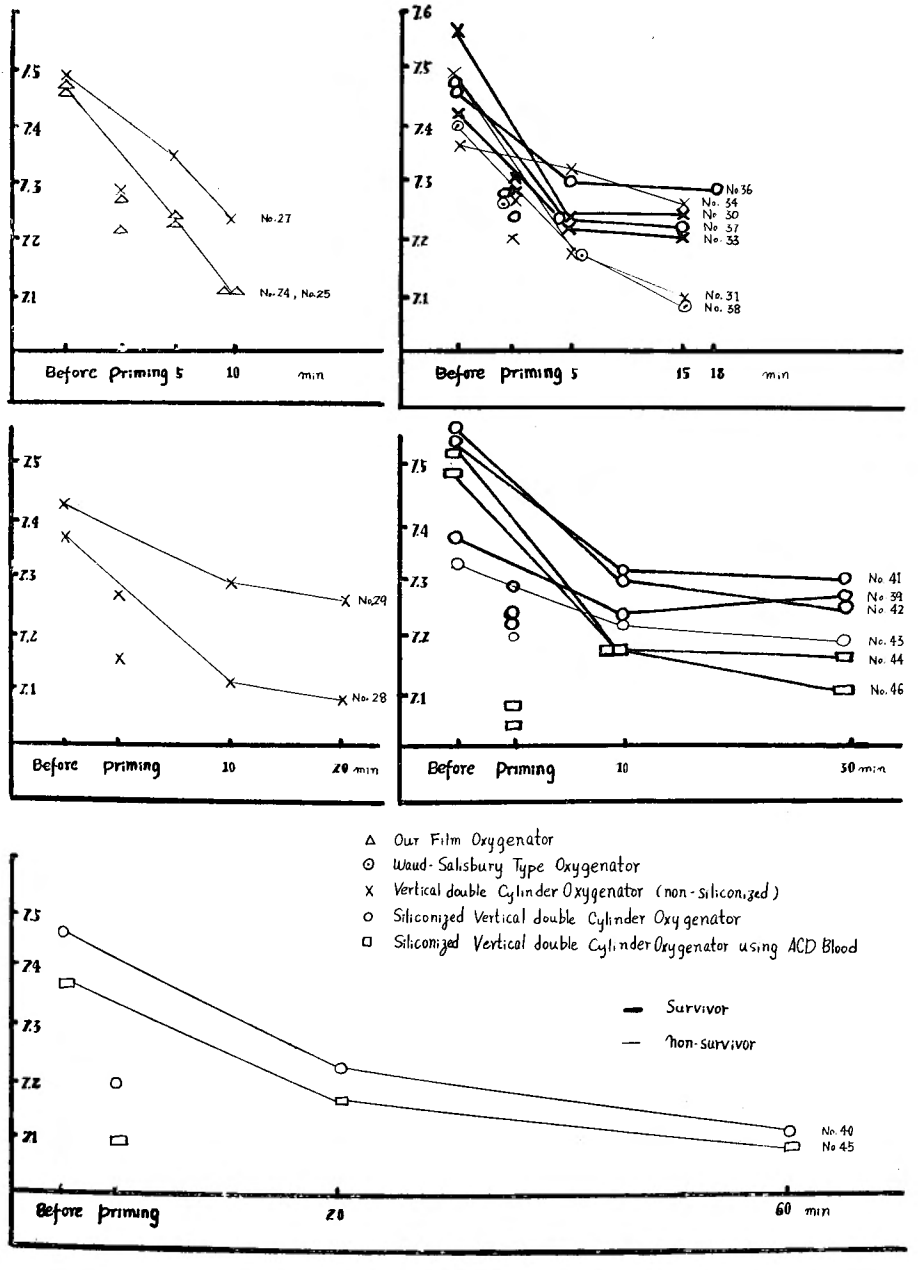
Fig. 18 Carbon Dioxide Content during Rerfusion



before perfusion (Fig. 18). This is due to voluntary hyperventilation. Therefore, as LITWIN,[26] BECHERL[27] and HUCKABEE[28] proved, this may lead to large lactate accumulations. When the perfusion began, the carbon dioxide content in arterialized blood in the oxygenator decreased slightly or remarkably.

As seen in this figure 18, in the animals showing excessive decrease in carbon dioxide content, the survival rate was low as a general rule, excepting in the animals

Fig. 19 pH Value during Perfusion

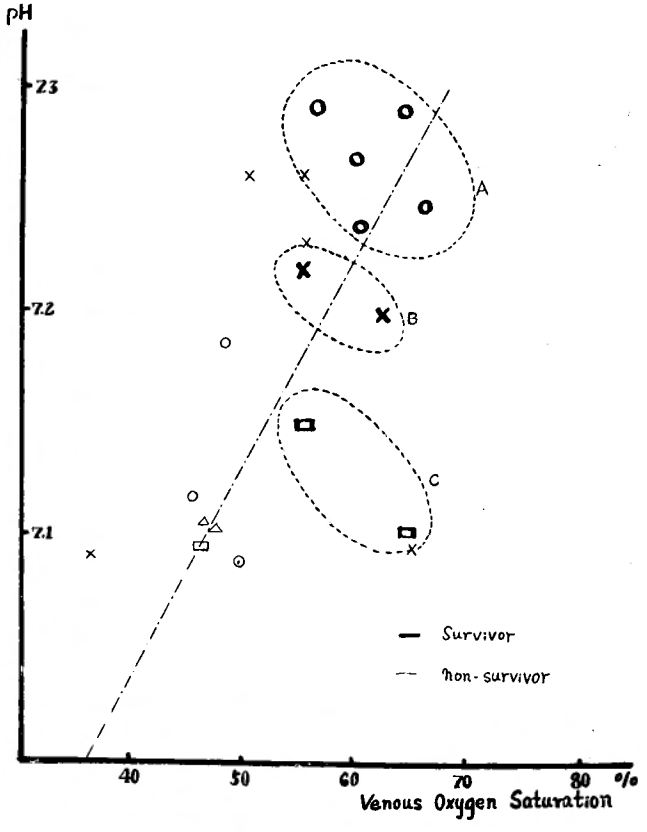


using ACD blood. This hypocapnia during perfusion may be largely responsible for the development of metabolic acidosis, as PONTIUS[29] pointed out.

(G) The pH of arterial blood :

As shown in Fig. 19, in case of 10-minutes perfusion using our film oxygenator the arterial blood pH was lowered to as low as 7.10, and in the case of 15-minutes perfusion using the WAUD-SALISBURY type foam oxygenator, the pH was lowered to as low as 7.09. When ACD blood was used, the pH value at the end of 30-minutes perfusion remained at about 7.13 on the average, though the priming blood had already been lowered to as low as 7.15 on the average, i. e. to the acidic side. Even in one dog of 60-minutes perfusion, the drop of pH value remained at 7.09, furthermore, the animals using ACD blood awakened more quickly and more vividly than did the animals in which ACD blood was not used. Moreover, as shown in Fig. 20, the arterial blood

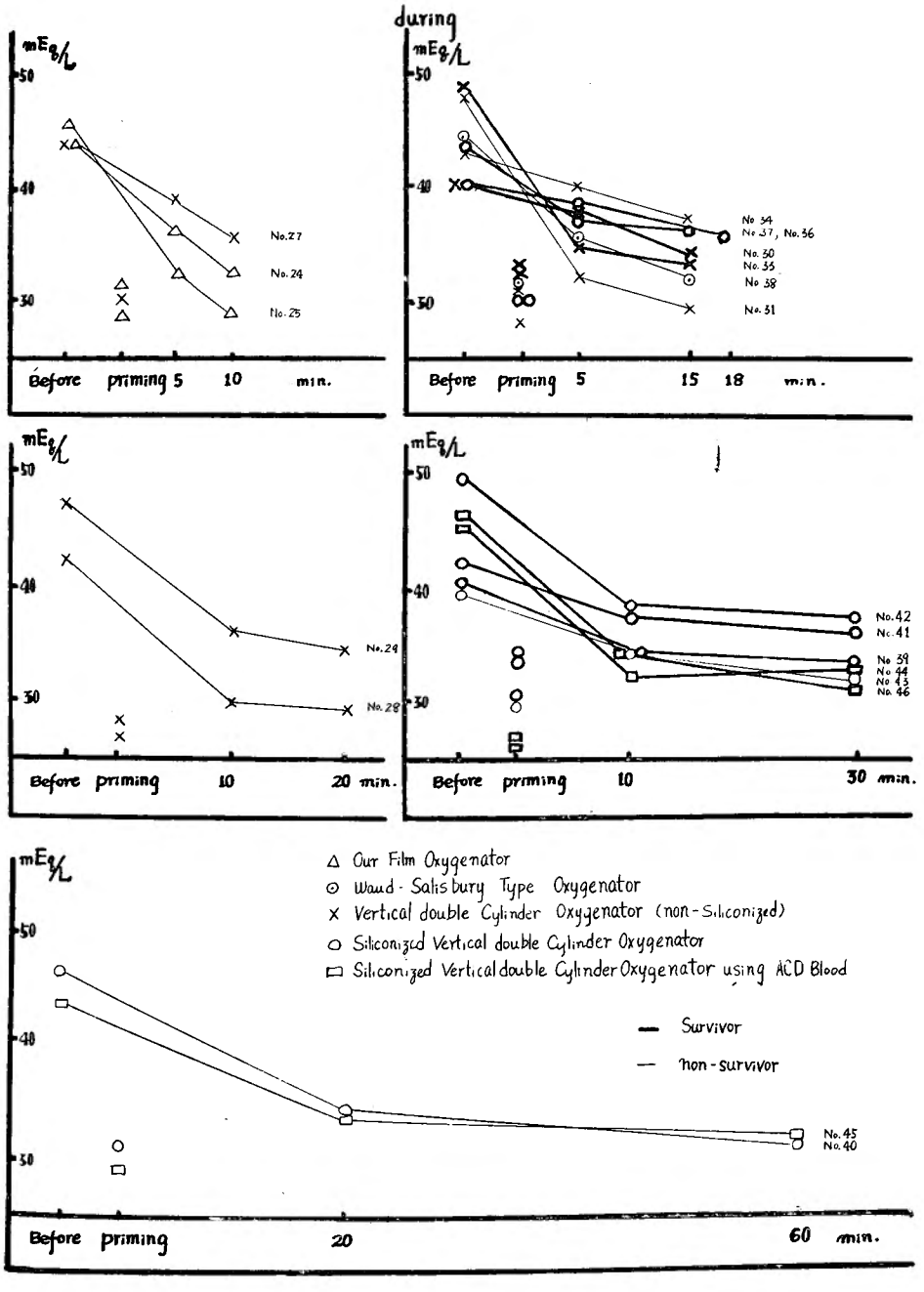
Fig. 20 Relationship between Arterial Blood pH and Venous Oxygen Saturation



pH interrelated to the oxygen saturation of mixed venous blood with a linear relationship. Here, it seems to be interesting that, as described in the figure 20, the pH value of the group using the siliconized vertical-double-cylinder oxygenator (Circle A) was the highest of all the survivors. The group using non-siliconized vertical-double-cylinder oxygenator (Circle B) somewhat low, but they were distributed around the correlation

line drawn in this figure from the lower left to the upper right. However, the animals using ACD blood with the siliconized vertical-double-cylinder oxygenator (Circle C) were not particularly distributed around this line, and they slipped off to the right lower part, that is, though the venous oxygen saturation was more than 55 %, the pH values shifted to the acidic side.

Fig. 21 Buffer Base during Perfusion



(H) Buffer base :

The values in buffer base, as shown in Fig. 21, decreased markedly during perfusion in every dog. It is important to prevent the priming blood from reduction of the buffer base as much as possible, because the animals would be seriously affected simultaneously with the start of perfusion by the priming blood, in which buffer base decreased to as little as 28-35 mEq/L as estimated in this Fig. 21, which resulted from leaving the priming blood at room temperature for two to three hours prior to operation; moreover, in the priming blood with addition of ACD solution, the values in buffer base decreased most markedly. Only three dogs showed decrease of less than 30 mEq/L at the end of perfusion. Considering the relation between buffer base deficit and flow rate it seems too hasty to conclude that the more the flow rate is, the less is the decline in buffer base deficit, and that the animals never survive when the value in buffer base decreases to such a large extent, because the animals survived for long periods in spite of such a decrease as to -15 mEq/L. Moreover, though the perfusion time protracted as in Fig. 22 (b), in contrast to Fig. 22 (a), there was no great difference between the two and

Fig. 22 (a) Relation between Buffer Base Deficit and Flow-rate 10～15minutes Perfusion

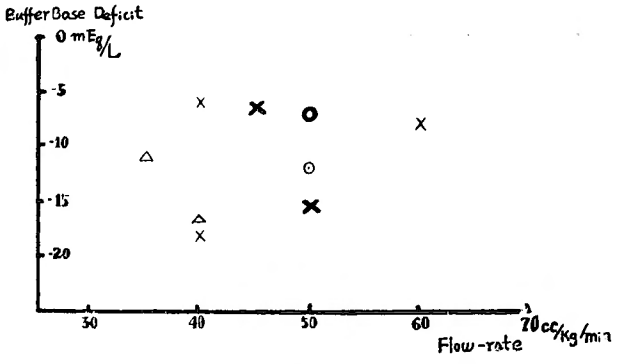
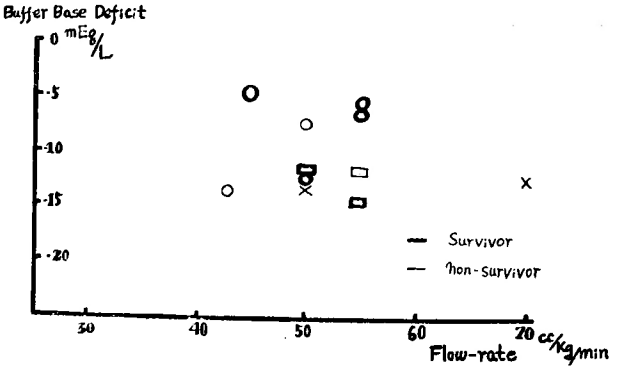


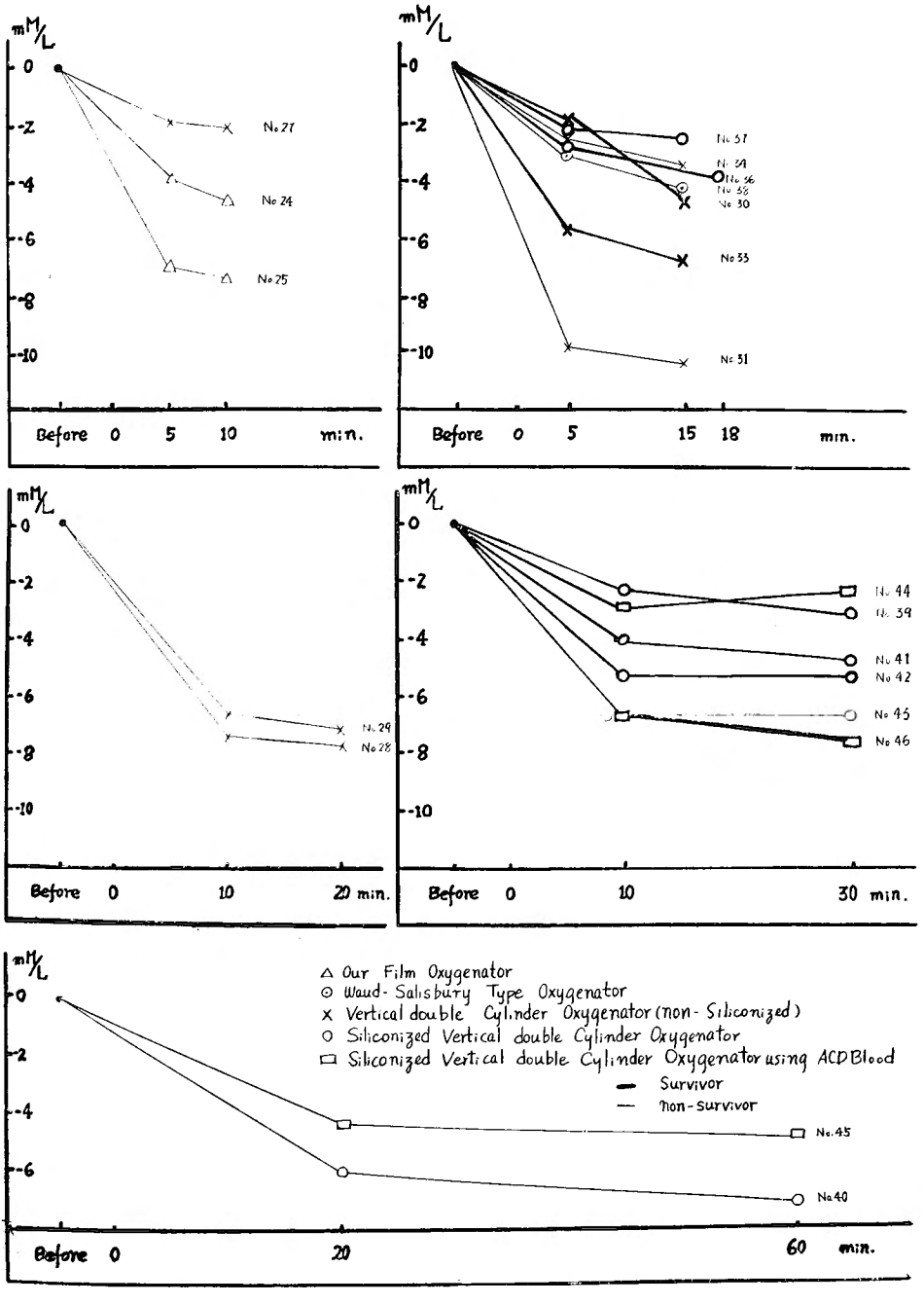
Fig. 22 (b) 18～60 minutes Perfusion



this fact seems to be more or less due to the improved technique employed and to the promotion of oxygenation-efficiency in the oxygenator.

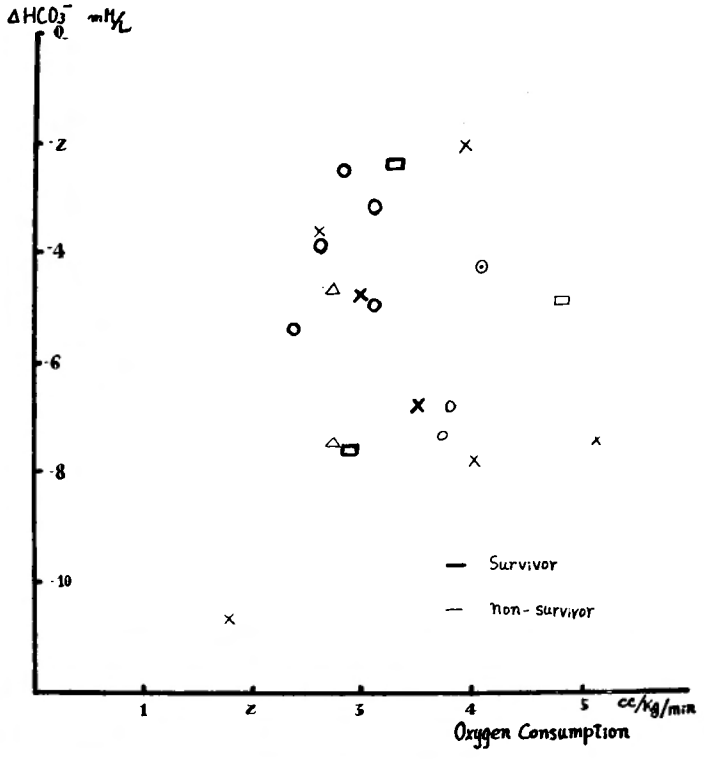
(I) Base bicarbonate :

Fig. 23 Bicarbonate Deficit during Perfusion



When we examined the acid-base equilibrium from the viewpoint of base bicarbonate, HCO_3^-, the value of bicarbonate deficit did not exceed -10.5 mM/L as the maximum, as shown in Fig. 23. Generally speaking, even when long continued perfusion was made, the values of bicarbonat deficite did not exceed -8mM/L. A linear relationship between bicarbonate deficit and oxygen consumption was not apparently noted, as in Fig. 24,

Fig. 24 Relationship betweeen Bicarbonate deficit and Oxygen Consumption



but all the survivors are in the upper portion of the figure, that is to say, the lowering of bicarbonate deficit was little as compared with the oxygen consumption.

However, the longer the perfusion time, the nearer each value will probably be to this dotted line.

(J) Lactic acid :

As shown in Fig. 25, when our film oxygenator was used, the rate of increase in lactic acid was high. The level of lactic acid in the priming blood had already increased considerably, therefore it is important that we check increase in lactic acid in the priming blood as much as possible.

Moreover, when the siliconized vertical-double-cylinder oxygenator was used, the rate of increase in lactic acid was generally lower than when the non-siliconized vertical-double-cylinder oxygenator was used. At the end of perfusion, the values of lactic acid in the surviving animals were about 40-50 mg/dl, The rise in the value of lactate, which was

Fig. 25 Lactic Acid during Perfusion

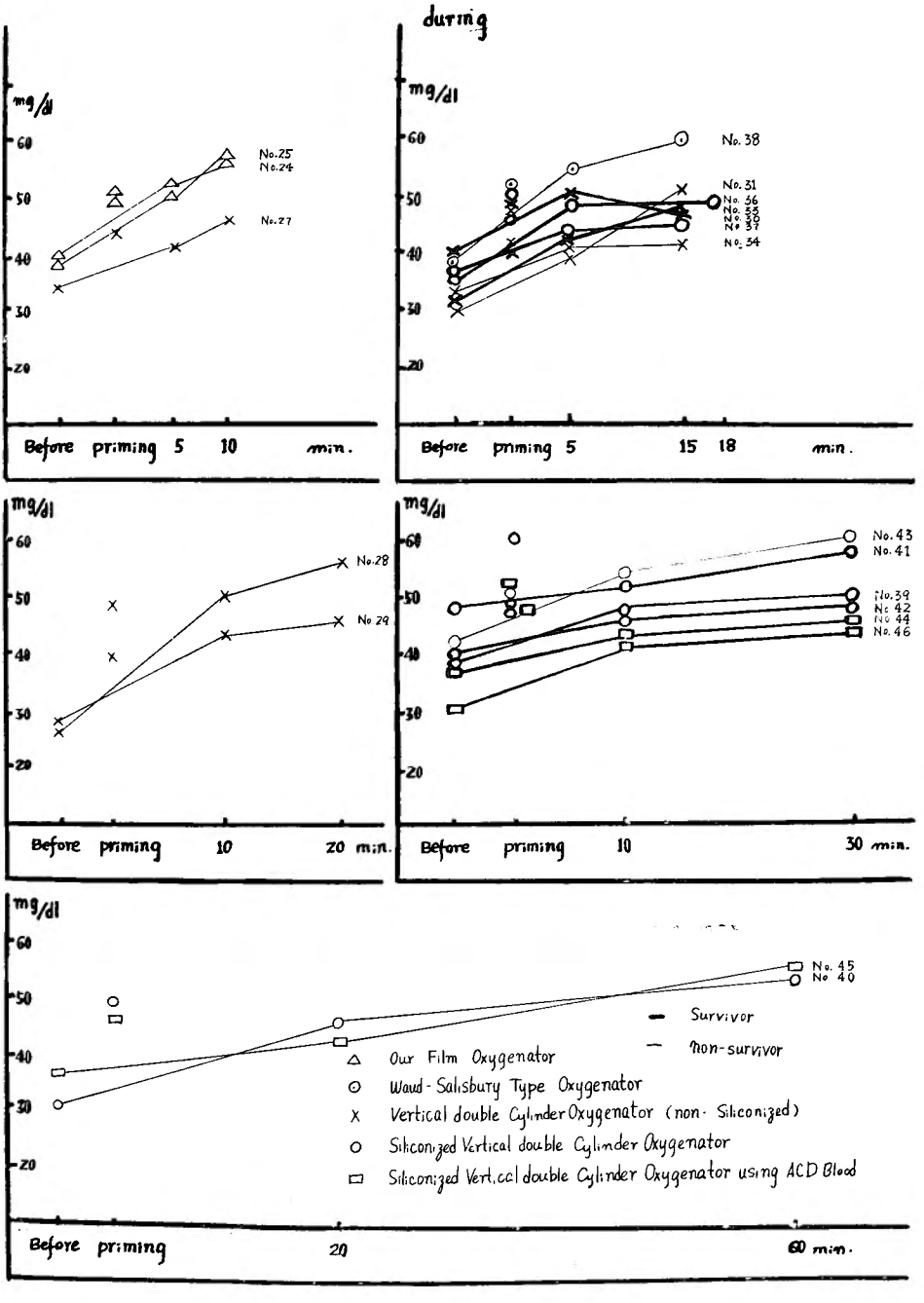
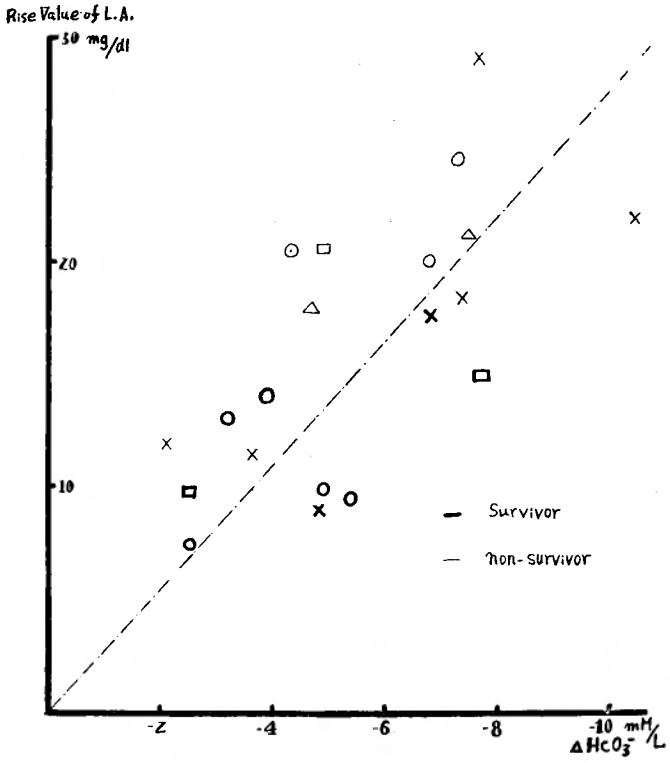


Fig. 26 Relationship between Bicarbonate Deficit and Rise of Lactic Acid



estimated using as standard the control value of pre-perfusion, was the lowest when the vertical-double-cylinder oxygenator was used. And, as shown in Fig. 26, an approximate linear correlationship was observed between the risen value of lactate and the bicarbonate deficit.

(K) Pyruvic acid :

The level of pyruvic acid continued increasing in almost cases, in accordance with the increase of the level of lactic acid, as shown in Fig. 27.

Most of the levels of pyruvic acid in the surviving animals were less than 3.8 mg/dl at the end of perfusion.

(L) Lactate-pyruvate ratio :

As in Fig. 28, L/P ratio[30, 31] was less than 20 in all the animals. Particularly in all the survivors, the L/P ratio did not exceed 15, that is, there were no cases of extreme reduction to hypoxia. When our film oxygenator was used, the increase in L/P ratio was considerably sharp. When ACD blood was used, the L/P ratio of 30-minutes perfusion was the lowest as compared with the L/P ratio of other 30-minutes perfusions.

(M) Blood sugar :

The blood sugar level increased continuously simultaneously with perfusion, but when ACD blood was used the blood sugar level rather tended to slight decrease in the latter half of perfusion (Fig. 29).

Fig. 27 Pyruvic Acid during Perfusion

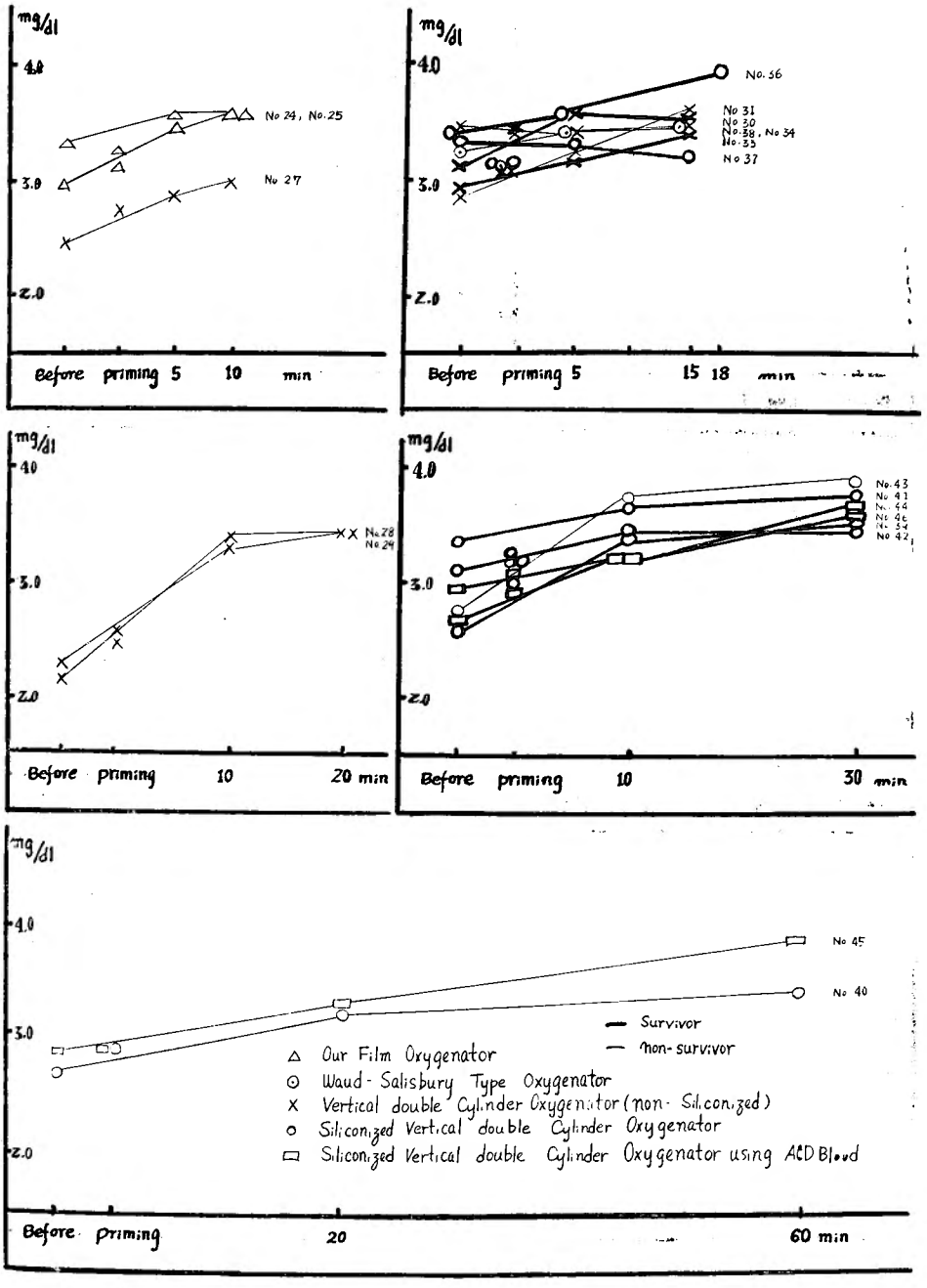


Fig. 28 Lactate-Pyruvate Ratio during Perfusion

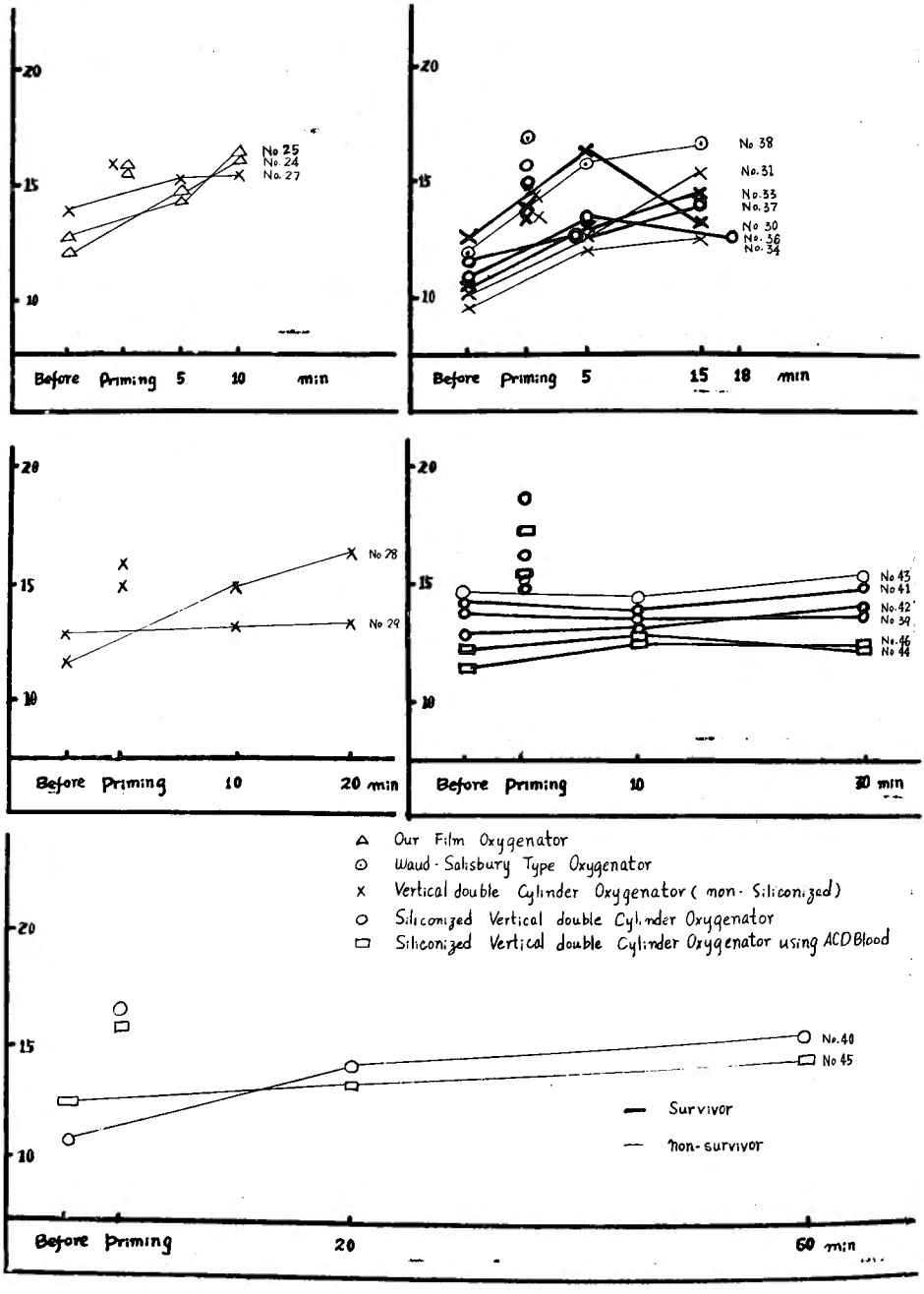


Fig. 29 Blood Sugar during Perfsion

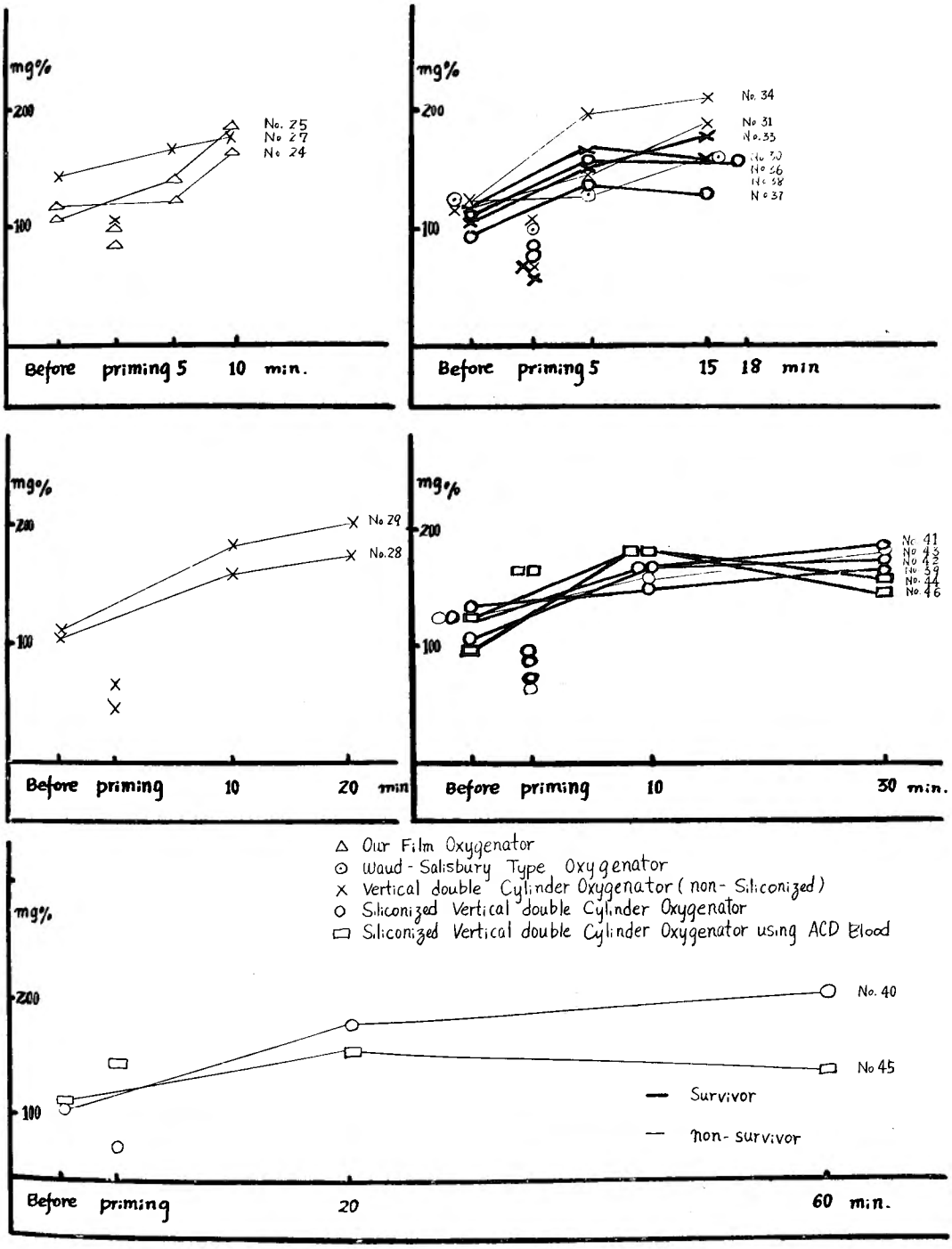
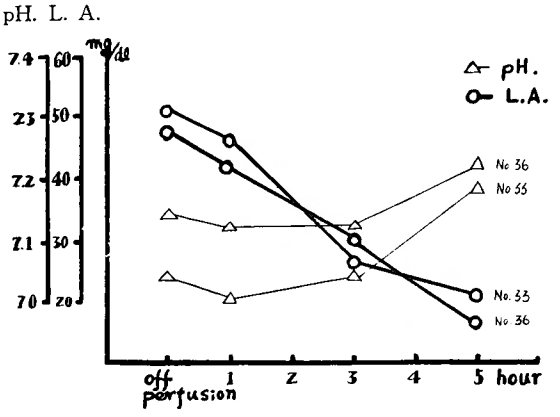


Fig. 30 Changes of Venous Blood pH and Lactic Acid after Perfusion



(N) Changes in pH-values and lactic acid in venous blood after perfusion :

The changes in pH-value and lactic acid level were observed until after 5 hours by measurement of the venous blood drawn through a thin polyethylene tube inserted through the femoral vein into the inferior vena cava. As shown in Fig. 30, in the surviving animals, the lactic acid level in the venous blood decreased little by little and after five hours returned almost to the control value of preperfusion. But, the pH value of venous blood showed little tendency of recovery until after three hours, but after five hours it trended toward returning to the control value.

DISCUSSION

As regard the cause or prevention of hemorrhage following the open-heart surgery using a pump-oxygenator, relatively few reports[32, 33, 34] are found. ABE reported in detail on the changes of blood constituents during or after perfusion. He stated that siliconization of the surface, in direct contact with blood, of the apparatus, the circuit and the collecting bottles, prevented completely the perfusate from postperfusion hemorrhage. Moreover, the addition of ε-aminocaproic acid and PVP solution in the priming blood led to good awakening and the inhibition of hypersecretion or hypersalivation. When our film oxygenator and the WAUD-SALISBURY type foam oxygenator were used, many fibrin-clots stuck to the inner surface of these instruments. TATSUTA,[35] who is the author's co-worker, observed a picture of embolism by fibrin-clots in the liver, kidney and spleen in his histological examinations.

The occurrence of fibrin-clots may lead to reduction of fibrinogen and promotion of the bleeding tendency. PHILLIPS[36] and PRICHARD[37] reported that hypofibrinogenemia is caused by increase in fibrinolytic activity by plasmin and leads to bleeding tendency. The use of ε-aminocaproic acid appeared to inhibit the phenomenon of fibrinolysis.[38] HENDLEY[39] stated that hypoxia increases permeability, decreases vascular resistance and induces the tendency of edema formation. But, the results of our studies showed that, even when hypoxia was present, the tendency toward edema formation was hardly noted, probably due to the action of ε-aminocaproic acid and PVP solution.

MALONEY[25] et al. stressed that ACD blood is worthy of use for clinical extracorporeal circulation from biochemical and hematologic points of view.

This is in line with the finding from the present studies. In our experiments all the animals were perfused at a comparatively low flow rate by use of the smaller sized venous catheters, therefore, the metabolic acidosis developed remarkably. As CROSS and KAY,[40] DIETTERT,[41] BEER,[42] ZENKER[43] and LILLEHEI[44] stated, changes in priming blood had great effects upon the development of metabolic acidosis during perfusion. KIRKLIN,[45] GROSS,[46] GIBBON[47] and ANDERSEN[48] poined out the importance of high flow rates of perfusion to prevent the development of metabolic acidosis which is often apt to occur at low flow rates. According to DONALD,[49] however, though the subjects were perfused at flow rate nearly like cardiac output, it was impossible to maintain the arterial pressure at a normal level. During the bypass, even at high perfusion rates, the arterial pressure lowers and the tissues are not adequately oxygenated and anaerobic oxidation takes place. Hypoxia in the peripheral tissues reduces pH-values and causes metabolic acidosis as CRAFOORD,[50] SENNING,[51] KIRKLIN,[45] DENNIS,[52] MENDELSOHN[40] and LILLEHEI[53] reported.

From the micro-circulatory standpoint, TAKEDA[54] studied biomicroscopically the state of peripheral circulation in omentum capillary. Under these circumstances, lactic and pyruvic acid levels rise gradually in the blood.

But this is corrected by bicarbonate, phosphate and hemoglobin buffer systems. As LITWIN and DEWALL[55] pointed out, decrease in base bicarbonate indicates an excess of organic acids which neutralize these buffers.

COFFIN and ANKENEY[56] noted that the rise in blood lactate and pyruvate level during perfusion which produced a metabolic acidosis was stoichiometrically interrelated to the bicarbonate fall. In this author's result, the risen levels in blood lactic acid which is the greater part of the fixed acids was linearly related to the bicarbonate deficit. In this report, during the bypass, the pH-values were maintained at higher than 7.20 by the oxygenator to eliminate carbon dioxide, and as LITWIN[57] showed, the pH-values at the end of perfusion were linearly related to the venous oxygen saturation. Furthermore, it is very interesting that when the siliconized vertical-double-cylinder oxygenator was used the pH-values were maintained highest at the end of perfusion, but when the ACD blood was used the pH-values were lowered remarkably even in the survivors. The relationship of flow rate to acidosis was shown by PONTIUS[58] and CLOWES.[59] PONTIUS showed that the changes in buffer base ranged from -6.4 to -2.1 mEq/L when perfusion rates were increased from 20 to 30 cc/kg/min to 60 to 150 cc/kg/min and the acidosis became more progressive when perfused with less than 40 cc/kg/min. CALLAGHAN[60] and MOORE[61] demonstrated that when in order to compensate metabolic acidsis a constant pH was maintained by eliminating CO_2 during perfusion, fall in pH and rise in CO_2 took place immediately after perfusion. Our results showed that the acidosis was purely metabolic and was not due to respiratory. However, the tendency of recovery was apparently observed after 5 hours in the surviving animals. Acidosis must be looked for 3 to 6 hours after the perfusion, as KOLFF and ITO[62] pointed out.

It is late acidosis which may often cause "sudden deaths" after perfusion. BARONOFSKY[63] thought that this sudden death might be due to an elevation of serum K and that

pH-values alone were unreliable as an index of post-perfusion acidosis, because of respiratory and blood buffer compensation, and he considered that a progressive drop in base bicarbonate, even with normal pH-values, was an indication of a progressive metabolic acidosis.

To alleviate this metabolic acidosis, it will be necessary that sodium bicarbonate be added during perfusion, with oxygen added carbon dioxide as the oxygenating gas, and that high flow rates are used.

CONCLUSION

In order to examine the causes of bleeding or shock-like state, improvement of the apparatus itself, the circuit and the method of the preparation of priming blood was made in turn, and whether the experimental animals could be kept alive for long periods (more than 48 hours) after partial or total perfusion was experimentally studied and the following conclusion was obtained.

(1) Siliconization of all inner side of the apparatus, the circuit and the collecting bottles prevented the animals from bleeding during or after perfusion.

(2) By addition of ε-aminocaproic acid and PVP solution into the priming blood, hyper-secretion and hypersalivation completely disappeared and the animals awakened more quickly and more vividly after perfusion.

(3) By use of cutting current, the bleeding from the chest wall or the wound of operation was completely prevented.

(4) Rapid hypothermia by A-A shunt was performed, coming to the following conclusions.

(a) The superiority of our pulsatile pump was proved, because it could keep the animals alive for long periods after 133-minutes partial perfusion by A-A shunt.

(b) All the animals with cannulation into the right carotid artery survived for long periods and all the other animals with cannulation into the left carotid artery died in shock-like state.

(c) All the data obtained of pH, buffer base, base bicarbonate, lactic acid, pyruvic acid and lactate-pyruvate-ratio in the animals with cannulation into the right carotid artery were better than in the animals with cannulation into the left carotid artery.

(d) The premedication performed was effective to keep out the occurrence of the ventricular fibrillation and the increase of blood viscosity.

(5) Total body perfusion was performed and the effectiveness of three kinds of oxygenators was compared, and finally we succeeded in all the 30-minutes total perfusion. The following conclusions were obtained.

(a) The arterial oxygen saturation in the animals with the use of film oxygenator declined remarkably despite 10-minutes perfusion, and in animals with the use of vertical-double-cylinder oxygenator the saturation was more than 90 % despite 60-minutes perfusion.

(b) A linear relationship between oxygen consumption and flow rate was noted, but it is not always the case that the survival rate becomes higher in proportion to the oxygen consumption.

(c) Mixed venous oxygen saturation in the survival cases was more than 55 % with the flow rate of 45-55 cc/kg/min, therefore the venous oxygen saturation is a factor having a great effect on the survival rate.

(d) The arterial blood pH-values of all survivors were not lowered to less than 7.20. When pH-value was lowered to as low as 7.10, the survival rate was not high, excepting the cases using ACD blood. Moreover, a linear relationship between arterial blood pH and mixed venous oxygen saturation was noted, but when the siliconized vertical-double-cylinder oxygenator was used, the pH-values were the highest of all, and when the non-siliconized vertical-double-cylinder oxygenator was used, the pH-values were low in some degree.

In the surviving animals using ACD blood, the pH-values were lower as compared with the mixed venous oxygen saturation, and the animals awakened most promptly and vividly.

(e) Buffer base decreased markedly simultaneously with the start of the perfusion, being influenced by the priming blood. Though remarkable metabolic acidosis developed, e g. -15 mEq/L in buffer base deficit, the animals survived for long periods without any accident.

(f) In the surviving animals bicarbonate deficit amounted to -8 mM/L, and a linear relationship was not apparently noted between bicarbonate deficit and oxygen consumption.

(g) The risen value of lactic acid was the lowest when the vertical-double-cylinder oxygenator was used, and a direct correlationship was approximately noted between the risen value of lactate and bicarbonate deficit.

(h) The increase in lactate-pyruvate-ratio was slight in all the surviving animals.

(i) After perfusion in the surviving animals, the value of lactate in the venous blood decreased gradually and returned almost to the control one of preperfusion after five hours. However, the pH-value of venous blood showed little tendency of recovery until after about three hours, but there was a probability of return to the control value after five hours.

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和文抄録

人工心肺装置による体外循環の実験的研究、特に血液ガス動態、酸塩基平衡、物質代謝変動に及ぼす影響に就いて

京都大学医学部外科学教室第2講座（指導：青柳安誠教授）
山崎英樹

われわれは当初脈動式動脈ポンプとWaud-Salisbury Foam Oxygenatorを使用して，完全体外循環による生存実験を施行したが，術中或は術後に出血傾向が出現したり，原因不明のショック様状態に陥つたり，また術後の覚醒も殆どなく，全例死亡した．そこでこの原因を解明する為に，人工心肺装置，回路，その充塡用血液の採取法及び保存法に就いて順次検討を加えた．

まず人工肺を使用しない人工心のみによる部分体外循環実験により，採血瓶，除泡器，金属カニューレにSilicon coatingを施し塩化ビニール管をシリコンゴム管に代える事によつて出血傾向は完全に消失した．

次に人工肺としてWaud-Salisbury Type Foam Oxygenatorを使用して部分体外循環実験を行つたところ，試獣は鼻咽腔からの分泌物が多くなり，又術後の覚醒も悪く原因不明のショック状態で死亡した．それでこの際人工肺中で毒性物質が産生されるものと考えて，その解毒の目的で，抗プラスミン剤及びPVP液を採血瓶に添加して採血したところ分泌亢進は消失し，術後の覚醒も良好となつた．しかしWaud-Salisbury Foam Oxygenatorの内面にfibrin塊附着が著明に認められたので，Silicon coatingしたガラス球を充満して一種のFilm Oxygenatorを作製して10分間部分循環を行つたところ，試獣は生存したが，やはりFibrinが可成り附着した．そこで直立二重円筒式人工肺（直二円式）を入手して25分間部分循環を行つたところPH値は0.1の下降にとどまり，Fibrin附着も少なくなり，試獣はよく生存した．故にその後の体外循環には主としてこの人工肺を使用した．次に人工肺を用いないA-A shuntによる急速中心冷却法を試みたところ左頸動脈に挿管した場合は全例死亡し，右頸動脈に挿管した2例は全て長期生存した．この際のPH, Buffer base, Base bicarbonate, 乳酸焦性ブドウ酸，L/P比等，すべて右頸動脈挿管例の方が良好であつた．尚急速中心冷却法で，部分体外循環とはいえ，全灌流時間133分間に及んでも何等の障碍も遺さずに生存した事は，われわれの脈動式動脈ポンプ及び回路

の優秀性を充分立証したものと考える.

そこで最後に人工肺に対する検討を行う目的で前記の三種類の人工肺を使用し，まず10分間の完全体外循環による生存実験から始めて逐次灌流時間の延長を計つた．即ち初め Film Oxygenator でも，又直二円式人工肺でも，試獣は術後胸腔内出血で全例死亡したが電気メス使用，集束結紮等で止血を完全に行う事により試獣は長期生存する様になつた．尚人工肺内面を Silicon coating する事により生存率は一層良好となり ACD 液を Priming Blood に添加してからは覚醒が全く良好となり，30分間完全体外循環例で1例の技術的過誤を除いて全例生存した．これ等の完全体外循環実験の中の20例に就いて血液ガス動態，酸塩基平衡，物質代謝変動を検討した結果は下記の如くである.

① Film Oxygenator の動脈血酸素飽和度は10分灌流に拘らず可成り下降したが直二円式では60分間灌流でも約90%程度にとどまり良好であつた.

② 動静脈血酸素較差は灌流終了時生存例で 4.7～7.0 vol % であつた.

③ 動静脈血炭酸ガス較差は灌流終了時生存例で 2.7～6.6 vol % であつた.

④ 酸素消費量は灌流量との間に直線的関係が認められたが，酸素消費量が多い程生存率が高いとは断言出来ない.

⑤ 生存例の混合静脈血酸素飽和度は灌流量45～55 cckg/min で55%以上であつた．故にこの静脈血酸素飽和度は生存率に影響を与える一つの示標と考えられる.

⑥ 動脈血炭酸ガス含量は灌流前より可成り減少しているが，灌流開始と同時に更に減少した.

⑦ 動脈血 PH の低下は生存例すべて7.2迄に止まつた．7.1 まで低下したものは生存率か悪かつたが，ACD 添加血使用例は例外であつた．又動脈血 PH と混合静脈血酸素飽和度との間には直線的関係を認めた．しかし Silicon coating した直二円式人工肺の PH が一番高く Non Coating のものはやや低値をとつた．ACD 添加血使用の生存例は混合静脈血酸素飽和度の割に PH は低い.

⑧ Buffer Base は灌流と同時に Priming Blood の影響を受けて著しく減少し Metabolic acidosis が顕著であつたが -15mEq/L の Buffer Base Deficit でも生存し得た.

⑨ Bicarbonate Deficit は -10mM/L 程度であつたが，生存例は -8mM/L までの低下にとどまつた．Bicarbonate Deficit と酸素消費量との間には特に直線関係が認めなかつた.

⑩ 乳酸値は直二円式が最も増加度が低く乳酸変動量と Bicarbonate Deficit との間に直線的関係を認めた.

⑪ 生存例の L/P 比は全て15以下に止まつた.

⑫ 血糖値は体外循環開始と同時に次第に増量の一途を辿るが，ACD 添加血使用例では後半稍々減少の傾向が見られた.

⑬ 生存例では灌流後静脈血乳酸値は時間と共に漸次減少し約5時間で灌流前値に復したのに対し，静脈血 PH は約3時間後迄は回復の傾向が余り認められなかつたが5時間後には回復の傾向が認められた.